UNITED STATES PATENT AND TRADEMARK OFFICE

**UNITED STATES DEPARTMENT OF COMMERCE**
**United States Patent and Trademark Office**
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/679,956 | 10/06/2003 | Marvin Siegel | 12071-002003 / SP-16 US D | 3565 |

26161 7590 03/08/2006

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

| EXAMINER | |
|---|---|
| LUCAS, ZACHARIAH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1648 | |

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

| Office Action Summary | Application No. | Applicant(s) |  |
|---|---|---|---|
|  | 10/679,956 | SIEGEL ET AL. |  |
|  | Examiner | Art Unit |  |
|  | Zachariah Lucas | 1648 |  |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *65-84* is/are pending in the application.

4a) Of the above claim(s) *72 and 74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-71,73 and 75-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of Group I; subinventions (A) (wherein the epitope is an MHC class I epitope), (2) (wherein the antigen is a viral antigen), and subinventions wherein the virus is a human papilloma virus (HPV); and of the species wherein the antigen is an HPV E7 antigen, the heat shock protein (Hsp) is Hsp65, and cells are derived from a spleen, in the reply filed on December 19,2005 is acknowledged. The Applicant traverses the restriction of Group I from Group I. The traversal is found persuasive, and the restriction is therefore withdrawn.

The Applicant further traverses the restriction among the methods drawn to determining the effects of fusion proteins comprising antigens from different human pathogens. The traversal is on the ground(s) that restriction practice is an improper basis to 'require applicants to rewrite the generic term "human pathogen" and instead limit claim 65 to a single virus.' This is not found persuasive because no such requirement is made. In particular, it is noted that the Requirement for Restriction indicated in paragraph 6 (page 6) that claim 65 is a linking claim and will be examined in accordance with the PTO linking claim practice as described in MPEP § 809.03. The Applicant's argument is therefore not found persuasive.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 72 and 74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in the reply filed on December 19, 2005.

3. Claims 65-71, 73, and 75-84 are under consideration.

## *Priority*

4. Applicant's claim for priority to prior applications 10/267,311, 09/613,303, and 60/143,757 is acknowledged.

## *Information Disclosure Statement*

5. The Information Disclosure Statement filed October 6, 2003 has not been fully considered. The Examiner has considered the patent references and references identified as ACCC-AOOO and ASSS-APPPP, ARRRR, ASSSS, and AYYYYYYY. However, the remaining references, cited in the parent applications, have been lost from the Office files. It would be appreciated if the Applicant could submit replacement copies of the other cited non-patent references such that they may be considered.

A copy of the IDS listing in which those references that have been considered are initialed is attached. The remaining references are crossed out as they have not yet been considered.

6. The following reference is in a foreign language accompanied by an English abstract. Due to this, the reference has been examined only to the extent of the disclosure in the abstract.

WO 97/26910- reference ACCC in the IDS listing.

## *Claim Rejections - 35 USC § 112*

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 65-71, 73, 75-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on methods for determining if a fusion protein stimulates a TH1-like response. However, it is not clear from the claims or the application what responses the Applicant considered to fall within the scope of Th1-like responses. The application indicates on page 19 that Th1-like responses can be detected through detection of IFN-γ or TNF-β expression, or of expression of the surface marker SLAM. However, the application also indicates that cytokine expression in general may be used. While each of IFN-γ, TNF-β, and SLAM appear to be generally considered as associated with Th1 responses (see e.g., U.S. 5,962,319, columns 3-4; and U.S. 5,576,423, column 1), cytokine production in general may be found in either Th1 or Th2 cells (see, U.S. 5,962,319, supra-indicating that other cytokines are associated with other, i.e. Th2, types of immune responses). It is therefore unclear what responses are included by the scope of the term "Th1-like."

For the purposes of the present action, a Th1-like response is read to include responses by cells that produce any cytokine normally associated with Th1 cells, including IFN-γ and TNF-β, or which expresses a surface marker such as SLAM.

## *Claim Rejections - 35 USC § 103*

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 65-69 and 76-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Lehmann et al. (U.S. 5,939,281) in view of the teachings of Young (U.S. 6,335,183- of record in the October 2003 IDS). These claims read on methods for determining if a fusion protein comprising all or a portion of a heat shock protein (hsp) fused to an antigen induces a Th1-like immune response. The methods comprise the steps of (a) providing a cell sample comprising naïve lymphocytes, esp., spleen cells, (b) providing the fusion protein, particularly where the hsp is Hsp65 from M. bovis, (c) contacting the cells with the fusion protein, and (d) determining if the fusion protein stimulates a TH1-like response. Claim 83 specifies that the determination step (d) is carried out through a determination of the expression of interferon-gamma (IFN-$\gamma$) by the cells. Claim 84 requires that the method is carried out with two fusion proteins, one comprising a complete hsp, the other comprising only a portion of the hsp.

Lehmann teaches a method for determining the type of a T cell response induced by an antigen, in particular through the detection of a cytokine in a test sample. See e.g., column 1 (lines 4-6), column 6 (lines 3-15). The reference teaches that determination of the type and magnitude of the cell response induced by an antigen is an important determination to be made for the identification of antigens against any particular type of infection. Column 2, lines 14-26.

The reference teaches that such a method would involve the provision of a cell culture of a primary cell population- including spleen cells, exposing the cells to an antigen, and determining if a particular cytokine is produced by the cells. Column 4 (lines 21-33) and columns 10-11. The reference also teaches that parallel assay may be run using controls. See esp., columns 10-11, crossover sentence. Finally, the reference also teaches that one means for the identification of the response being induced is to detect the expression of IFN-γ. See e.g., Column 3 (lines 18-21), columns 10-11 (esp., Table 1), and columns 1-2. However, while the reference teaches such a method, and indicates that the use of such a method for the determination of the type of immune response induced by any particular antigen is important (thereby suggesting the application of this method to identify the response induced by any antigen) the reference does not teach the application of such a method to fusion proteins as described by the present claims.

Young teaches the enhancement of immune responses against an antigen by fusing the antigen to a heat shock protein, including the hsp65 of M. bovis. See e.g., claims 1, and 3-5. The reference teaches that the fusion protein may include a viral antigen and the hsp, or a sufficiently large portion of the hsp to enhance the immune response against the antigen. Id., and columns 11-13. Further, the reference teaches that such fusion results in the ability of the fusion protein to induce a strong and specific B and T cell response. However, the reference does not teach what type of T cell response is induced by the fusion protein, nor the size of the portion of the heat shock protein needed to provide such a response. Thus, it would have been obvious to those of ordinary skill in the art to use the method of Lehmann to determine the type and strength of the immune response induced by the fusion proteins of Young. Further, it would also have been obvious to those of ordinary skill in the art to apply the method of Lehmann to determine the number of residues of the hsp required to enhance the immune response.

In addition to the teachings of Lehmann, other teachings in the art also indicate that the production of IFN-γ by T cells stimulated by hsp/antigen fusion proteins is associated with the induction of CTL responses. See e.g., Suzue et al., PNAS 94: 13146-51, at page 13150, right column (stating that the immunization of mice with the described hsp/antigen fusion protein exhibited "antigen-dependent production of IFN-γ, which implies the presence of the Th1 helper T cells and CTL"- reference of record in the October 2003 IDS). See also, Anthony et al. Vaccine 17:373-383, at page 381, right column (suggesting that hsp/antigen immunogenic activity may also be exerted through activation of other types of T cells, which cells also produce IFN-γ- reference also of record in the October 2003 IDS). Thus, while these other references indicate that the means by which the fusion proteins act is not known, they do indicate that IFN-γ production is produced by the activated cells, and is associated with the fusion proteins immunogenic activities. Thus, from these additional teachings, it would also have been obvious to those in the art to use the methods of Lehmann to either determine if a particular hsp/antigen fusion protein is an effective immunogen, or as a means to help in the determination as to how the hsp fusions operate.

Those of ordinary skill in the art would have had a reasonable expectation of success in the application of the Lehmann method to the fusion proteins of Young because Lehmann indicates that the method may be applied for the determination of the type of immune response induces by any antigen. Further, because the Young reference teaches that fusion to a hsp results in the ability of the antigen to induce both a T and B cell response, those in the art would have had sufficient motivation for the use of the method to identify the type of response being induced by the fusion proteins. In view of the teachings of Young that portions of the hsps may be used to induce the improved responses against the antigens, those of ordinary skill in the art would also have been motivated to used the method of Lehmann to compare the immune response induced by fusions comprising various fragments of hsps with antigens to those of a fusion comprising the full length hsp. Thus, the combined teachings of these references render the claimed methods of determining if a fusion protein induces a TH1-like response.

65-69 and 76-84

11. Claims 65-71, 73, and 75-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Mizzen et al. (WO 98/23735- of record in the October 2003 IDS) in view of the teachings of Lehmann et al. (U.S. 5,939,281). These claims have been described in part above. Claims 70, 71, 73, and 75 each require that the antigen is from a human papillomavirus E7 protein. Claim 75 additionally requires that the heat shock protein is an M. bovis Hsp65 protein.

Mizzen teaches methods for inducing CTL responses against antigens comprising the fusion of the antigens to heat shock proteins. Among the heat shock proteins identified as useful for such fusions is the M. bovis Hsp65 protein. See e.g., pages 42 and 45-46. The reference teaches the induction of such CTL responses for the treatment of or tumor or viral infections, and identifies as a potential target antigen the E7 protein. Pages 12 (lines 16-32), 14 (esp. lines 19-20), and 31 (esp. lines 8-23). Further, the reference teaches that CTL responses are induced through activation of Th1 cells, which cells are disclosed as producing interferon gamma. Page

17. The reference also discloses methods of testing fusion proteins for the ability to induce CTL responses through the detection of CTL activity. See e.g., Example 2, pages 39. The reference teaches that detection of such activity is a measure of the activation of the Th1 pathway. Page 17, lines 10-17. However, the reference does not teach a method for the determination of whether a fusion protein induces a Th1-like response through stimulation of naïve lymphocytes in vitro, or methods involving the detection of IFN-γ production.

However, as was described above, the Lehmann reference does teach such a method for determining if an antigen induces a Th1-like response. In view of the teaching of such a method by Lehmann, and the teachings in Mizzen that induction of the Th1 pathway results in a CTL response, it would have been obvious to those of ordinary skill in the art that the method of Lehmann would be a functional alternative to the methods described in the examples of Mizzen for determining if a fusion protein is capable of inducing a CTL response. Thus, it would have been obvious to those in the art to test the fusion proteins suggested by Mizzen using the method of Lehmann for the determination of whether the proteins induce a Th1-like response. The combined teachings of these references therefore render the claimed methods obvious.

It is noted that claim 68 describes a fusion protein comprising residues 1-200 of the Hsp65 from M. bovis. While the Mizzen reference does not teach a fusion protein comprising only these residues, the reference does teach that the M. bovis Hsp65 protein would be a useful hsp for use in the fusion proteins. The complete hsp would inherently contain this sequence. Further, the reference also indicates that portions of the hsp proteins may be used. It would therefore have been obvious to those in the art to construct various fusion proteins comprising various portions of the disclosed hsp proteins to determine if the portions would be capable of inducing the requisite immune responses. Thus, it would have been obvious to those in the art to test fusion proteins comprising any fragment of M. bovis Hsp65 using the method of Lehmann.

## *Double Patenting*

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 65-71, 73, and 76-84 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6, 7, 9-16 of U.S. Patent No. 6,495,347. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the patent do not include the limitations regarding the use of heterologous antigens including MHC class I or MHC class II epitopes, or the limitations relating to the size of the HSP as identified in claims 77-80 of the present application.

However, the claims of the patent do relate to the inclusion of heterologous peptides in the fusion proteins. The specification of the patent specifically indicates that the heterologous polypeptides may contain any amino acid sequence useful for the stimulation of an immune response, and indicates that preferable sequences include MHC class I or class II binding epitopes. Column 8, lines 41-45. The claims of the patent also relate to the use of all or a portion of the Hsp. The specification indicates that the fusion proteins may include portions of Hsps of the lengths identified in claims 77-80. Column 8, lines 29-34. In view of these teachings in the patent, the limitations added to the present claims represent obvious variations of the claims in the patent. The present claims are therefore rejected for obviousness type double patenting over the claims of the patent.

14. The above rejection is, in part, based on the specification of a previously issued patent, rather than the claims. In support of the use of this material, the examiner notes the following excerpt from MPEP section 804 II(B)(1):

> When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. This does not mean that one is precluded from all use of the patent disclosure.
>
> The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Thus, the courts have held that it is permissible to use the specification in determining what is included in, and obvious from, the invention defined by the claim on which the rejection is based. This is true even where elements are drawn from the specification describing the claimed invention which are not elements in the claim itself.

### *Conclusion*

15. No claims are allowed.

16. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Breloer et al., J Immunol 162: 3141-47 (of record in the October 2003 IDS). This reference appears to teach a method for the in vitro stimulation of naïve macrophages for Th1 activity (IFN-γ and TNF-α production). Pages 3141-42. However, while the reference teaches the stimulation of cells in vitro using heat shock proteins, it does not teach methods wherein the cells are stimulated with a fusion protein as described in the present claims, or the use of naïve lymphocytes as opposed to naïve macrophages.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

James C. Housel
1/23/06
JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

George C. Elliott
George C. Elliott, Ph.D
Director
Technology Center 1600